REMARKS

Claims 199-224 are pending. Claims 199, 200 and 215 are amended herein. Support for the amendment to claims are found throughout the Specification, as filed, and no new matter is presented by the amendment.

Favorable reconsideration in light of the amendments are remarks which follow a respectfully requested.

1. 35 U.S.C. §112 Rejections

Claims 199-224 are rejected under 35 U.S.C. 112, second paragraph.

The Office asserts that "lipid-like materials" is deemed indefinite because "it is unclear what lipids it represents. While Applicants respectfully disagree, Applicants have amended claims 199 and 215 to delete "lipid-like materials" and have replaced the term with "lipoids". Applicants respectfully submit that the terms "lipid" and "lipoid" are well-known terms that define natural substances having lipophilic groups, poor solubility in water and good solubility in organic solvents. Such substances are fats or fat-like substances, i.e. behave like fats. They are selected from, for example, triglycerides, phosphatides, sphyngolipids, steroids, carotinoids, etc. Applicants respectfully submit that in view of the general, well-known definition of "lipid" and "lipoid" and in view of the disclosure, one skilled in the art could readily determine the substances that fall under these terms.

The Office further asserts that the distinction between "surface-active substances" and "surfactants" is unclear. Applicants have deleted the term "surfactants". Accordingly, the rejection is moot.

The Office asserts the "the liquid medium" in the independent claims lacks antecedent basis. Applicants have amended the claim as required.

The Office asserts that claims 199 and 215 are confusing.

In particular, with respect to claim 199, the Office asserts that "the substrate is formed by a combination of one surface-building lipid and one surface destabilizing lipid". Applicants respectfully submit that claim 199 recites that first surface-building amphipathics substance is selected from lipids, whereas the second surface destabilizing amphipathic substance is selected from surface-active substances.

The Office further asks "If the surface built by one lipid is destabilized by the other lipid, then how can a substrate form by this combination and how can the third amphiphathic substance bind to the substrate? What is the nature of the substrate formed?"

Applicants refer to the description, for example, on page 6, line 8 wherein the nature of the substrates is described. It is set forth that the soft surfaces comprise a mixture of lipids and surfactants. The surfaces are formed by a blend of molecules forming a stable membrane and at least one strongly amphipathic bilayer-destabilizing component, which is exemplified by the mixture of phospholipids and surfactants. The resulting surface, thus, is basically formed by the (surface-building) lipids, with the surface-active molecules inserted into the surface. The insertion of surface-active molecules leads to a destabilization of the surface structure. The addition of surface-destabilizing substances consequently does not lead to the destruction, but only to a destabilization, which results in a higher deformability or adaptability of the surface. This permits the adsorbing macromolecules to get enriched near the adsorbent surface due to the locally attractive charge-charge and other interactions, and leads to an optimisation of non-electrostatic interactions/binding to the adsorbent surface. The presence of hydrophobic and H-bond binding-sites, which are generated or made accessible by surface-flexibility and/or adaptability, allows for this (see e.g. p. 6, lines 24 - 32). The insertion of surface-active substances into the lipid membranes, and the resulting adaptability of the surface, increases the proximity and number of the hydrophobic binding sites in/at the membrane solution interface. This is favourable, for example, in protein adsorption to a soft membrane surface (p. 7, lines 4 - 9).

Applicants have unexpectedly found that the adsorption of macromolecules to membrane surfaces can be optimised by increasing the adaptability of the surface by the addition of surface-active substances.

Regarding claim 200, Applicants have added the questioned claim terminology to claim 199 and have deleted it from claim 199. Thus, rejection of the claim is moot.

2. 35 U.S.C. §102 Rejections

WO 92/03122

Claims 199-224 are rejected under 25 U.S.C. §102(b) as being anticipated by WO 92/03122.

Applicants respectfully traverse.

Applicants teach a composition comprising a substrate in a liquid medium, wherein the substrate is in the form of a bilayer membrane surface. The substrate comprises at least one first surface-building amphipathic and at least one second surface-destabilising amphipathic substance. The first substance is selected from lipids and lipoids capable of forming membrane bilayers, and the second substance is selected from surface-active substances and is more soluble than the first substance in the liquid medium. The composition further comprises at least one third amphipathic substance selected from insulin, interferon, interleukin, immunoglobulin and hormone. The substrate and the at least one third substance do not have opposite charges. The molecules of the third substance are associated with the substrate that is preformed by the first and second substances. The composition is formed by combining the first and second substances in contact with the liquid medium to form substrates and adding the at least one third amphipathic substance to the preformed substrates such that the molecules of the third substance to associate with the substrate.

Applicants further teach a method of producing a pharmaceutical composition comprising: selecting at least one first and at least one second substance, combining the first and second substances in contact with a liquid medium to form substrates in the form of bilayer membrane surfaces, selecting the at least one third substance, adding the at least one third substance to the substrates preformed by the at least one first and the at least one second substance, allowing the molecules of the third substance to associate with the substrate. The at least one first surface-building amphipathic substance is selected from lipids and lipoids capable of forming membrane bilayers. The at least one second surface-destabilising amphipathic substance is selected from surface-active substances that are more soluble in the liquid medium than the first substance. The at least one third amphipathic substance is selected from insulin, interferon, interleukin, immunoglobulin and hormone. Further, the substrate and the at least one third substance do not have opposite charges.

Applicants provide improved methods and compositions that optimize and control macromolecular association to a bilayer membrane surface. Applicants unexpectedly discovered that amphiphats (macromolecules) adsorb to soft surfaces comprising a mixture of lipids and surface-active substances more efficiently than to lipid aggregates containing no surface active substances. Applicants further unexpectedly discovered that the relative number of bound amphiphatic macromolecules is higher for surfaces which bear net charges with the same sign as the net charge of the adsorbing amphiphatic macromolecules. This is contradictory to the current teachings that electrostatic binding requires opposite charges on the interacting entities in order to provide strong bonds. This is further contradictory to the widely accepted teachings that surfactants suppress protein binding. This is further contradictory to the belief that soft membranes are more hydrophilic and mutually repulsive than their less adaptable kind.

Applicants discovered that by combining the first and the second substance in liquid medium **before** adding the third substance, a highly adaptable membrane surface substrate can be formed which provides improved association of the third substance. The adsorption promoting capability of the adsorbent surface permits the third substance: i) to get enriched near the adsorbent surface, due to the locally attractive charge-charge and other interactions; ii) to

optimise non-electrostatic interactions/binding to the adsorbent surface (which typically requires the presence of hydrophobic and H-bond binding sites, which are generated or made accessible by surface-flexibility and/or adaptability). See page 6, lines 25-32 of the Specification. This feature is achieved by combining the three substances in the order above.

WO 92/03122, does not teach or suggest each and every element of Applicants' claims. WO 92/03122 exclusively refers to the incorporation of macromolecules into the vesicles formed by such surfaces. Examples 163 – 166, referred to by the Office, describe systems incorporating the active agent. According to Examples 163 - 165, the mixtures are treated for 60 minutes with ultrasound, which causes a continuous dissolution and formation of vesicles, which leads to the incorporation of the inulin in the vesicles. In Example 166, the suspensions are pressed through a filter, which also leads to the dissolution and reformation of the vesicles. These Examples illustrate what is mentioned in the description of WO 92/03122 on p. 145, par. 3, namely that "it may be advantageous, if the incorporation of the agent is carried out after the carrier formation" (engl. translation of citation).

Thus, WO 92/03122 does not teach or suggest a substrate in a liquid medium, wherein the substrate is in the form of a bilayer membrane surface, comprising at least one first surface-building amphipathic substance selected from lipids and lipoids capable of forming membrane bilayers, and at least one second surface-destabilising amphipathic substance selected from surface-active substances, to which molecules of a third amphipathic substance selected from insulin, interferon, interleukin, immunoglobulin and hormone, are associated.

Further, WO 92/03122 does not teach or suggest a method of producing a pharmaceutical composition comprising wherein at least one first and at least one second substance are combined in contact with a liquid medium to form substrates in the form of bilayer membrane surfaces, and adding at least one third substance to the preformed substrates such that the molecules of the third substance associate with the substrate. Rather, according to WO 92/03122 active agent is incorporated into vesicles. As set forth, methods of WO 92/03122 add the active agent to the mixture of vesicle forming substances, and the vesicle formation is induced

subsequently such that the active agent being present in the liquid medium is incorporated into the vesicles, i.e. the active agent represents the filling of the vesicles. The alternative method described in the above-mentioned Examples are carried out under extreme conditions leading to continuous dissolution and reformation of vesicles and, thus, to the incorporation of the agent inside of the vesicles.

In contrast to this, the present preparations are formed by mixing the vesicle suspensions with the third substance. Applicants avoid applying any methods as drastic as ultrasonication or filtration which would lead to dissolution of the preformed vesicles. As set forth above, dissolution leads to incorporation of the third substance into the vesicles, which is avoided in the present invention. This is explicitly mentioned on p. 23, last par., where it is stated that the association of the third substance to the adsorbing surface may be assisted by agitation, mixing or incubation, provided that such treatment does not break-up the preformed surfaces. Applicants further note that Examples 153 - 154 of the present patent application are comparative examples.

As provided in MPEP-2131, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

As set forth above, WO 92/03122 does not teach a substrate in a liquid medium, wherein the substrate is in the form of a bilayer membrane surface (comprising at least one first surface-building amphipathic substance selected from lipids and lipoids capable of forming membrane bilayers, and at least one second surface-destabilising amphipathic substance selected from surface-active substances) to which molecules of a third amphipathic substance selected from insulin, interferon, interleukin, immunoglobulin and hormone, are associated. Rather, WO 92/03122 describes vesicles into which macromolecules are incorporated. The macromolecules are not adsorbed to the surface of the vesicles. Such a composition is different than and possesses different properties than the compositions taught by Applicants.

Accordingly, claims 199 and 215 are not anticipated by WO 92/03122. Claims 200-214 and 216-224 depend from claims 199 and 215 and, likewise, are not anticipated by WO 92/03122.

Weder (US 4,731,210)

Claims 199-208 are rejected under 35 U.S.C. §102(b) as being anticipated by Weder (US 4,731,210). Applicants respectfully traverse.

Weder describes a process wherein associates of at least one amphiphilic bilayer-forming substance and a solubilizing agent are formed in an aqueous phase. The equilibrium conditions for the molar ratio of bilayer-forming substance to solubilizing agent in the associates are then changed in the aqueous phase containing the associates, in order to remove solubilizing agent from the associates, so that the associates combine to form liposomes. Thus, the liposomes of Weder do not contain solubilizing agent, which is removed in order to form the liposomes.

As mentioned in the Abstract and expressly set forth in col. 3, lines 20 to 27 of Weder, "the present invention is based on the discovery that associates from which the solubilizing agent is removed combine to form liposomes, the size of which depends on the rate at which the solubilizing agent is withdrawn or, more fundamentally, on the rate at which the equilibrium conditions are changed to effect an increase in the molar ratio of bilayer-forming substance to solubilizing agent in the associates".

Thus, the systems disclosed in Weder are not based on a combination of bilayer-forming substances and solubilizing substances, but on the removal of the solubilizing agent, which leads to the desired compositions. The removal of solubilizing agent, which is the decisive step in preparing the compositions of Weder, is described in detail from col. 5 to col. 8, wherein each of the methods described results in removal of the solubilizing agent from the associates.

In addition, Weder does not teach or suggest the association/adsorbtion of pharmaceutical substances to surfaces formed by at least one first surface-building amphipathic substance and at

least one second surface-destabilising amphipathic substance. Rather, according to Weder, in some embodiments, the bilayer-forming substance itself can be a pharmaceutical substance (see Abstract). Thus, in this embodiment, the pharmaceutical substance forms the bilayer, it is not a substance that is associated or adsorbed to the bilayer surface as taught by Applicants.

In another embodiment, the pharmaceutical substances and/or pharmaceutical auxiliaries are **ab**sorbed or incorporated into the liposomes (see claim 4, Example 2), which does not mean **ad**sorption or association according to the present invention. According to Weder, the pharmaceutical substance is added to the bilayer-forming substance and solubilizing agent during the preparation process, which leads to the incorporation of the pharmaceutical substance into the liposomes. As set forth in Example 2, "defined enrichment of the substances added in the aqueous phase containing the liposomes and, if a suitable temperature is chosen, an increased absorption of these substances into the liposomes is thereby made possible." (col. 14, lines 9 - 14). Also, in Example 1, it is set out that "Further preparations of homogeneous unilamellar liposomes of varying size... in some cases with incorporation of lipophilic and hydrophilic model pharmaceutical substances" are obtained (col. 12, 11, lines 9 - 14).

Thus, Weder clearly does not teach or suggest a pharmaceutical composition comprising a substrate in the form of a bilayer membrane surface formed by at least one first surface-building amphipathic substance and at least one second surface destabilizing amphipathic substance in a liquid medium. Rather, according to Weder, liposomes are formed by a bilayer-forming substance alone after removal of solubilizing agent, which is not part of the final composition. Furthermore, Weder describes the incorporation of the substance into the liposomes and does not teach or suggest the association/adsorption of the substance to the surface of the liposomes. Still further, the third substance is added to the "resultant" liposomes, i.e to such liposomes from which the surface-active substance has been removed (claim 4) , or is added during formation of the liposomes absorbing or incorporating the substance therein.

Accordingly, claim 199 is not anticipated by Weder. Claims 200-208 depend from claim 199 and, likewise, are not anticipated by Weder.

3. 35 U.S.C. §103 Rejections

WO 92/03122 and Uster

Claims 199-224 are rejected under 35 U.S.C. §103(a) over WO 92/03122 alone or in combination with Uster (US 4,944,948).

Applicants respectfully traverse.

As set forth above, WO 92/03122 does not teach or suggest the association of the active agent with the outside of the surface of the vesicles. Rather, according to WO 92/03122, the agent is incorporated inside of the vesicles. Further, WO 92/03122 does not teach or suggest that such association is possible and, if so, how it could be achieved.

Uster does not remedy these deficiencies. As stated by the Examiner, Uster describes an interaction wherein negative charge on a vesicles enables the EGF molecules (which are positively charged) to adsorb on the surface of the vesicles. This is due to simple electrostatic interactions, and has nothing to do with the present invention, which is based on the adaptability of the surfaces formed by the first and second substances, which leads to the enrichment of the adsorbing macromolecules near the adsorbing surface and the optimisation of the non-electrostatic interactions/binding to the adsorbent surface (see p. 6, lines 24 - 32). Uster also does not teach or suggest increasing the proximity and number of hydrophobic binding sites in/at the membrane solution interface, which is described on p. 7, lines 4 – 9 of the present disclosure. Furthermore, the teaching of Uster contradict with the those of the present invention. In particular, Applicants have discovered that that the relative number of bound amphipathic macromolecules is unexpectedly higher even for the surfaces which have net charges with the same sign as the net charge of the adsorbing entity (p. 6, lines 17 - 20). Uster, on the other hand, relies upon electrostatic interactions between negatively charged vesicles and positively charged molecules.

In sum, WO 92/03122 exclusively deals with the incorporation of a substance into vesicles and does not teach or suggest the association of molecules with the outer surface of vesicles nor that such association is possible. Uster, describe a process wherein negative charge on the vesicles enables the EGF molecules (which is positively charged) to adsorb on the surface of the vesicles. This is due to simple electrostatic interactions. No combination of these references teaches or suggests Applicants' invention.

Accordingly, claims 199 and 215 are patentable over WO 92/03122 and Uster. Claims 200-214 and 216-224 depend from claims 199 and 215 and, likewise, are patentable over WO 92/03122 and Uster.

WO 92/03122 and Weder

Claims 199-224 are rejected under 35 U.S.C. 103(a) over Weder (4,731,210) by itself or in combination with WO 92/03122.

Applicants respectfully traverse.

As set forth above, WO 92/03122 does not teach or suggest the association of the macromolecules with the outside of the surface of the vesicles. Further, WO 92/03122 does not teach or suggest that such association is possible and, if so, how it could be achieved.

As further set forth above, Weder clearly does not teach or suggest a pharmaceutical composition comprising a substrate in the form of a bilayer membrane surface formed by at least one first surface-building amphipathic substance and at least one second surface destabilizing amphipathic substance in a liquid medium. Rather, according to Weder, liposomes are formed by a bilayer-forming substance alone after removal of solubilizing agent, which is not part of the final composition. Furthermore, like WO 92/03122, Weder describes the incorporation of the substance into the liposomes and does not teach or suggest the association/adsorption of the substance to the surface of the liposomes. Still further, according to Weder, the third substance is not added after the formation of the liposomes, but, rather, is added during formation of the liposomes, or after the removal of the surface-active substance

Accordingly, claims 199 and 215 are patentable over WO 92/03122 and Wederr. Claims 200-214 and 216-224 depend from claims 199 and 215 and, likewise, are patentable over WO 92/03122 and Weder.

4. Double Patenting

Application 09/621,574

Claims 199-224 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 31, 38 and 70-76 of copending Application 09/621,574.

Claims 199-224 are also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-66, 80-81, 88-100 of copending Application 10/357,618.

Applicants respectfully traverse.

The present claims are directed to a pharmaceutical composition and methods for making a pharmaceutical compositon comprising (i) a substrate in the form of a bilayer membrane surface comprising: at least one first surface-building amphipathic substance selected from lipids and lipoids capable of forming membrane bilayers, and at least one second surface-destabilising amphipathic substance selected from surface-active substances, in a liquid medium, wherein the second substance is more soluble than the first substance in the liquid medium, and (ii) at least one third amphipathic substance selected from insulin, interferon, interleukin, immunoglobulin and hormone, the molecules of the third substance associated with the substrate.

The present claims are directed to a pharmaceutical composition and methods for making a pharmaceutical compositon comprising (i) a substrate in the form of a bilayer membrane surface comprising: at least one first surface-building amphipathic substance selected from lipids and lipoids capable of forming membrane bilayers, and at least one second surface-destabilising

amphipathic substance selected from surface-active substances, in a liquid medium, wherein the second substance is more soluble than the first substance in the liquid medium, and (ii) at least one third amphipathic substance selected from insulin, interferon, interleukin, immunoglobulin and hormone, the molecules of the third substance associated with the substrate.

The claims of application 09/621,574, on the other hand, are directed to a preparation suitable for transporting active agents through permeability barriers. The preparation comprises a plurality of transfersomes in a medium, and comprise a pharmaceutically acceptable lipid and a pharmaceutically acceptable surfactant which is compatible with the lipid. The ratio lipid to surfactant enables the transfersomes to undergo sufficient deformation to enable the transfersomes to pass as an entity through a permeability barrier which has pores smaller than the size of said transfersomes. The total concentration of lipid in the medium is from about 0.1% to about 30%, by weight and the ratio of lipid to surfactant is from about 5.5:1 to about 1:500.

Thus, the present claims are clearly distinguishable over those in application 09/621,574. The claims of application 09/621,574 do not teach or suggest a composition comprising (i) a substrate in the form of a bilayer membrane surface formed by at least one first surface-building amphipathic substance and at least one second surface-destabilising amphipathic substance and (ii) molecules of at least one third amphipathic substance associated with the substrate.

The claims of application 10/357,618 are directed to preparations for application, administration or transport of an active ingredient into and through the pores in semi-permeable barriers or other constrictions. The preparation is in the form of mixed amphipat aggregates with extended surface (ESAs). The ESAs are formed by a combination of at least one first amphipatic component (membrane forming component MFC), at least one second amphipatic component (membrane destabilising component MDC), and at least one third (membrane destabilising component MDC) amphipatic component, suspended in a suitable liquid medium.

Thus, the present claims are clearly distinguishable over those in application 10/357,618. The claims of application 10/357,618 do not teach or suggest a composition comprising (i) a

substrate in the form of a bilayer membrane surface formed by at least one first surface-building amphipathic substance and at least one second surface-destabilising amphipathic substance and (ii) molecules of at least one third amphipathic substance associated with the substrate.

Thus, the present claims are distinguishable over those of applications 09/621,574 and 10/357,618. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

It is respectfully submitted that the subject application is in a condition for allowance. Early and favorable action is requested. Applicant(s) believe(s) that additional fees are not required. However, if for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, the Commissioner is hereby authorized and requested to charge Deposit Account No. **04-1105**.

Respectfully submitted

Date: September 27, 2005

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